

CENTER FOR DRUG EVALUATION AND RESEARCH

Approval Package for:

Application Number : 074674

Trade Name : ACYCLOVIR 200MG CAPSULES

Generic Name: Acyclovir 200mg Capsules

Sponsor : Zenith Goldline Pharmaceuticals, Inc.

Approval Date: April 22, 1997

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION 074674

CONTENTS

	Included	Pending Completion	Not Prepared	Not Required
Approval Letter	X			
Tentative Approval Letter				
Approvable Letter				
Final Printed Labeling	X			
Medical Review(s)				
Chemistry Review(s)	X			
EA/FONSI				
Pharmacology Review(s)				
Statistical Review(s)				
Microbiology Review(s)				
Clinical Pharmacology Biopharmaceutics Review(s)				
Bioequivalence Review(s)	X			
Administrative Document(s)				
Correspondence				

CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 074674

APPROVAL LETTER

Zenith Goldline Pharmaceuticals, Inc.
Attention: Karen Rocco
140 Legrand Avenue
Northvale, NJ 07647
|||||

APR 22 1997

Dear Madam:

This is in reference to your abbreviated new drug application dated May 22, 1995, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Acyclovir Capsules, 200 mg.

Reference is also made to your amendment dated April 2, 1997.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly the application is approved. The Division of Bioequivalence has determined you Acyclovir Capsules, 200 mg to be bioequivalent and, therefore, therapeutically equivalent to the listed drug (Zovirax® Capsules, 200 mg of Glaxo Wellcome, Inc.). Your dissolution testing should be incorporated into the stability and quality control program using the same method proposed in your application.

Under 21 CFR 314.70, certain changes, in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81. The Office of Generic Drugs should be advised of any changes in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print. Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-240). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call you attention to 21 CFR 314.81 (b) (3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug marketing, Advertising, and Communications (HFD-240) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours.

(b)4 - Confidential

Business

Douglas L. Sporn

Director

Office of Generic Drugs

Center for Drug Evaluation and Research



4-22-87

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074674

FINAL PRINTED LABELING

MARGO

Zenith Goldline

NDC 0172-4266-60

**ACYCLOVIR
CAPSULES**

200 mg

100 CAPSULES (White)

Store between 15° and 25°C (59° and 77°F).
CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

PROTECT FROM LIGHT AND MOISTURE

NDC 0172-4266-60

Each Capsule Contains:
Acyclovir 200 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309



N 3 0172-4266-60 5

LOT: APR 22 1997
EXP:

Zenith Goldline

NDC 0172-4266-70

**ACYCLOVIR
CAPSULES**

200 mg

500 CAPSULES (White)

Store between 15° and 25°C (59° and 77°F).
CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

PROTECT FROM LIGHT AND MOISTURE

NDC 0172-4266-70

Each Capsule Contains:
Acyclovir 200 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309



N 3 0172-4266-70 4

LOT: APR 22 1997
EXP:

Zenith Goldline

NDC 0172-4266-80

**ACYCLOVIR
CAPSULES**

200 mg

1000 CAPSULES (White)

Store between 15° and 25°C (59° and 77°F).
CAUTION: Federal law prohibits dispensing without prescription.

USUAL DOSAGE: See Package Insert

PHARMACIST: Dispense in a tight, light-resistant container as defined in the USP. Use child-resistant closure (as required).

PROTECT FROM LIGHT AND MOISTURE

NDC 0172-4266-80

Each Capsule Contains:
Acyclovir 200 mg

Manufactured by:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309



N 3 0172-4266-80 3

LOT: APR 22 1997
EXP:

101e

levels; there was a statistically significant decrease in the group mean numbers of corpora lutea, total implantation sites and live fetuses in the F1 generation. Although statistically significant, there was no dose-related decrease in group mean numbers of live fetuses and implantation sites at 12.5 mg/kg/day and 25 mg/kg/day, s.c. The intravenous administration of 100 mg/kg/day, a dose known to cause obstructive nephropathy in rabbits, caused a significant increase in fetal resorptions and a corresponding decrease in litter size (plasma levels were not measured). However, at a maximum tolerated intravenous dose of 50 mg/kg/day in rabbits (53 to 106 times human levels), no drug-related reproductive effects were observed. Intrauterine doses of 80 or 320 mg/kg/day acyclovir given to rats for 6 and 1 months, respectively, caused testicular atrophy. Plasma levels were not measured in the one-month study and were 24 to 48 times human levels in the six-month study. Testicular atrophy was persistent through the 4-week postdose recovery phase after 320 mg/kg/day; some evidence of recovery of sperm production was evident 30 days postdose. Intravenous doses of 100 and 200 mg/kg/day acyclovir given to dogs for 31 days caused aspermatogenesis. At 100 mg/kg/day plasma levels were 47 to 94 times human levels, while at 200 mg/kg/day they were 159 to 317 times human levels. No testicular abnormalities were seen in dogs given 50 mg/kg/day i.v. for one month (21 to 41 times human levels) and in dogs given 60 mg/kg/day orally for one year (6 to 12 times human levels).

Pregnancy

Teratogenic Effects: Pregnancy Category C

Acyclovir was not teratogenic in the mouse (450 mg/kg/day, p.o.), rabbit (50 mg/kg/day, s.c. and i.v.) or in standard tests in the rat (50 mg/kg/day, s.c.). These exposures resulted in plasma levels 9 and 18, 16 and 106, and 11 and 22 times, respectively, human levels. In a non-standard test in rats, there were fetal abnormalities, such as head and tail anomalies, and maternal toxicity.⁴² In this test, rats were given 3 s.c. doses of 100 mg/kg acyclovir on gestation day 10, resulting in plasma levels 63 and 125 times human levels. There are no adequate and well-controlled studies in pregnant women. Acyclovir should not be used during pregnancy unless the potential benefit justifies the potential risk to the fetus. Although acyclovir was not teratogenic in standard animal studies, the drug's potential for causing chromosomal breaks at high concentration should be taken into consideration in making this determination.

Nursing Mothers

Acyclovir concentrations have been documented in breast milk in two women following oral administration of acyclovir and ranged from 0.6 to 4.1 times corresponding plasma levels (3.4). These concentrations would potentially expose the nursing infant to a dose of acyclovir up to 0.3 mg/kg/day. Caution should be exercised when acyclovir is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients less than 2 years of age have not been adequately studied.

ADVERSE REACTIONS

Herpes Simplex

Short-Term Administration

The most frequent adverse events reported during clinical trials of treatment of genital herpes with orally administered acyclovir were nausea and/or vomiting in 8 of 298 patients (2.7%) and headache in 2 of 298 (0.6%). Nausea and/or vomiting occurred in 2 of 287 (0.7%) patients who received placebo. Less frequent adverse events, each of which occurred in 1 of 298 patient treatments with orally administered acyclovir (0.3%), included diarrhea, dizziness, anorexia, fatigue, edema, skin rash, leg pain, inguinal adenopathy, medication taste and sore throat.

Long-Term Administration

The most frequent adverse events reported in a clinical trial for the prevention of recurrences with continuous administration of 400 mg (two 200 mg capsules) 2 times daily for 1 year in 586 patients treated with acyclovir were: nausea (4.8%), diarrhea (2.4%), headache (1.9%) and rash (1.7%). The 589 control patients receiving intermittent treatment of recurrences with acyclovir for 1 year reported diarrhea (2.7%), nausea (2.4%), headache (2.2%) and rash (1.5%). The most frequent adverse events reported during the second year by 380 patients who elected to continue daily administration of 400 mg (two 200 mg capsules) 2 times daily for 2 years were headache (1.5%), rash (1.3%) and paresthesia (0.8%). Adverse events reported by 329 patients during the third year include asthenia (1.2%), paresthesia (1.2%) and headache (0.9%).

Herpes Zoster

The most frequent adverse events reported during three clinical trials of treatment of herpes zoster (shingles) with 800 mg of oral acyclovir 5 times daily for 7 to 10 days in 323 patients were: malaise (11.5%), nausea (8.0%), headache (5.9%), vomiting (2.5%), diarrhea (1.5%), and constipation (0.3%). The 323 placebo recipients reported malaise (11.1%), nausea (11.1%), headache (11.1%), vomiting (2.5%), diarrhea (0.3%) and constipation (2.4%).

Chickenpox

The most frequent adverse events reported during three clinical trials of treatment of chickenpox with oral acyclovir in 495 patients were: diarrhea (2.2%), abdominal pain (0.6%), rash (0.6%), vomiting (0.6%), and flatulence (0.4%). The 498 patients receiving placebo reported: diarrhea (2.2%), flatulence (0.8%) and insomnia (0.4%).

Observed During Clinical Practice

Based on clinical practice experience in patients treated with oral acyclovir in the U.S., spontaneously reported adverse events are uncommon. Data are insufficient to support an estimate of their incidence or to establish causation. These events may also occur as part of the underlying disease process. Voluntary reports of adverse events which have been received since market introduction include:

General

Fever, headache, pain, peripheral edema, and rarely, anaphylaxis

Nervous

Confusion, dizziness, hallucinations, paresthesia, seizure, somnolence (These symptoms may be marked, particularly in older adults.)

Digestive

Diarrhea, elevated liver function tests, gastrointestinal distress, nausea

Hemic and Lymphatic

Leukopenia, lymphadenopathy

Musculoskeletal

Myalgia

Skin

Alopecia, pruritus, rash, urticaria

Special Senses

Visual abnormalities

Urogenital

Elevated creatinine

OVERDOSAGE

Patients have ingested intentional overdoses of up to 100 capsules (20 g) of acyclovir, with no unexpected adverse effects.

Precipitation of acyclovir in renal tubules may occur when the solubility (2.5 mg/mL) in the intratubular fluid is exceeded. Renal lesions considered to be related to obstruction of renal tubules by precipitated drug crystals occurred in the following species: rats treated with i.v. and i.p. doses of 20 mg/kg/day for 21 and 31 days, respectively, and at s.c. doses of 100 mg/kg/day for 10 days; rabbits at s.c. and i.v. doses of 50 mg/kg/day for 13 days; and dogs at i.v. doses of 100 mg/kg/day for 31 days. A 6 hour hemodialysis results in a 60% decrease in plasma acyclovir concentration. Data concerning peritoneal dialysis are incomplete but indicate that this method may be significantly less efficient in removing acyclovir from the blood. In the event of acute renal failure and anuria, the patient may benefit from hemodialysis until renal function is restored. See **DOSEAGE AND ADMINISTRATION**.

DOSEAGE AND ADMINISTRATION

Treatment of Initial Genital Herpes

200 mg (one 200 mg capsule) every 4 hours, 5 times daily for 10 days

Chronic Suppressive Therapy for Recurrent Disease

400 mg (two 200 mg capsules) 2 times daily for up to 12 months, followed by re-evaluation. See **INDICATIONS AND USAGE** and **PRECAUTIONS** for considerations on continuation of suppressive therapy beyond 12 months. Alternative regimens have included doses ranging from 200 mg 3 times daily to 200 mg 5 times daily.

Intermittent Therapy

200 mg (one 200 mg capsule) every 4 hours, 5 times daily for 5 days. Therapy should be initiated at the earliest sign or symptom (prodrome) of recurrence.

Acute Treatment of Herpes Zoster

800 mg (four 200 mg capsules) every 4 hours orally 5 times daily for 7 to 10 days.

Treatment of Chickenpox

Children (2 years of age and older)

20 mg/kg per dose orally 4 times daily (80 mg/kg/day) for 5 days. Children over 40 kg should receive the adult dose for chickenpox.

Adults and children over 40 kg

800 mg four times daily for 5 days.

Therapy should be initiated at the earliest sign or symptom of chickenpox to derive the maximal benefits of therapy.

Patients with Acute or Chronic Renal Impairment

Comprehensive pharmacokinetic studies have been completed following intravenous acyclovir infusions in patients with renal impairment. Based on these studies, dosage adjustments are recommended in the following chart for genital herpes and herpes zoster indications.

Normal Dosage Regimen	Creatinine Clearance (mL/min/1.73 m ²)	Adjusted Dosage Regimen	
		Dose (mg)	Dosing Interval
200 mg every 4 hours	>10	200	every 4 hours, 5x daily
	0-10	200	every 12 hours
400 mg every 12 hours	>10	400	every 12 hours
	0-10	200	every 12 hours
800 mg every 4 hours	>25	800	every 4 hours, 5x daily
	10-25	800	every 8 hours
	0-10	800	every 12 hours

Hemodialysis

For patients who require hemodialysis, the mean plasma half-life of acyclovir during hemodialysis is approximately 5 hours. This results in a 60% decrease in plasma concentrations following a six-hour dialysis period. Therefore, the patient's dosing schedule should be adjusted so that an additional dose is administered after each dialysis.^{45,46}

Peritoneal Dialysis

No supplemental dose appears to be necessary after adjustment of the dosing interval.^{47,48}

HOW SUPPLIED

Acyclovir capsules are available as white opaque hard gelatin capsules, spin printed "4266" on the cap and "200" on the body, containing 200 mg acyclovir packaged in bottles of 100, 500 and 1000 capsules. PHARMACIST: Dispense in a light, light-resistant container as defined in the USP. Use child-resistant closure (as required). PROTECT FROM LIGHT AND MOISTURE. Store between 15° and 25°C (59° and 77°F). CAUTION: Federal law prohibits dispensing without prescription.

REFERENCES

- O'Brien JG, Campoli-Richards DM. Acyclovir - an updated review of its antiviral activity, pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1989;37:233-309.
- Littler E, Zeuthen J, McBride AA, et al. Identification of an Epstein-Barr virus-coded thymidine kinase. *EMBO J* 1986;5(8):1959-1966.
- Miller WH, Miller RL. Phosphorylation of acyclovir (acycloguanosine) monophosphate by GMP kinase. *J Biol Chem* 1980;255:7204-7207.
- Furman PA, St Clair MH, Fyfe JA, et al. Inhibition of herpes simplex virus-induced DNA polymerase activity and viral DNA replication by 9-(2-hydroxyethoxymethyl)guanine and its triphosphate. *J Virol* 1979;32:72-77.
- Derse D, Cheng YC, Furman PA, et al. Inhibition of purified human and herpes simplex virus-induced DNA polymerases by 9-(2-hydroxyethoxymethyl)guanine triphosphate: effects on primer-template function. *J Biol Chem* 1981;256:11447-11451.
- McGuire PV, Shaw JE, Elion GB, et al. Identification of small DNA fragments synthesized in herpes simplex virus-infected cells in the presence of acyclovir. *Antimicrob Agents Chemother* 1984;25:507-509.
- Barry DW, Blum MR. Antiviral drugs: acyclovir. In: Turner P, Shand DG, eds. *Recent Advances in Clinical Pharmacology*, ed 3. New York: Churchill Livingstone, 1983: chap 4.
- DeLencoe E. Comparative efficacy of antihelminths in different cell lines. *Antimicrob Agents Chemother* 1982;21:651-663.
- McLaren C, Ellis MN, Hunter GA. A colorimetric assay for the measurement of the sensitivity of herpes simplex viruses to antiviral agents. *Antiviral Res* 1983;3:223-234.
- Barry DW, Nussinoff-Lehman S. Viral resistance in clinical practice. Summary of five years experience with acyclovir. In: Kono R, Nakajima A, eds. *Herpes Viruses and Virus Chemotherapy (Ex Med Int Congr Ser 667)*. New York: Excerpta Medica, 1985:269-270.
- Dekker C, Ellis MN, McLaren C, et al. Virus resistance in clinical practice. *J Antimicrob Chemother* 1983;12(suppl B):137-152.
- Sibrack CD, Gutman JT, Willett CM, et al. Pathogenicity of acyclovir-resistant herpes simplex virus type 1 from an immunodeficient child. *J Infect Dis* 1982;146:673-682.
- Crumpacker CS, Schnepf LE, Marlowe SJ, et al. Resistance to antiviral drugs of herpes simplex virus isolated from a patient treated with acyclovir. *N Engl J Med* 1982;306:343-346.
- Wade JC, Newton B, McLaren C, et al. Intravenous acyclovir to treat mucocutaneous herpes simplex virus infection after marrow transplantation: A double-blind trial. *Ann Intern Med* 1982;96:265-269.
- Burns WH, Saral R, Santos GW, et al. Isolation and characterization of resistant herpes simplex virus after acyclovir therapy. *Lancet* 1982;1:421-423.
- Strauss SE, Takt H, Seidlin M, et al. Suppression of frequently recurring genital herpes: a placebo-controlled double-blind trial of oral acyclovir. *N Engl J Med* 1984;310:1545-1550.
- Collins P. Viral sensitivity following the introduction of acyclovir. *Am J Med* 1988;85(2A):129-134.
- Erich KS, Mills J, Chatis P, et al. Acyclovir-resistant herpes simplex virus infections in patients with the acquired immunodeficiency syndrome. *N Engl J Med* 1989;320(5):293-296.
- Hill EL, Ellis MN, Barry DW, et al. *28th Intersci Conf on Antimicrob Agents Chemother*. Los Angeles, 1988. Abst No 0840:260.
- Ellis MN, Keller PM, Fyfe JA, et al. Clinical isolates of herpes simplex virus type 2 that induces thymidine kinase with altered substrate specificity. *Antimicrob Agents Chemother* 1987;31(7):1117-1125.
- Collins P, Larder BA, Oliver NM, et al. Characterization of a DNA polymerase mutant of herpes simplex virus from a severely immunocompromised patient receiving acyclovir. *J Gen Virol* 1989;70(3):375-382.
- Field HJ, Darby G, Wildy P. Isolation and characterization of acyclovir-resistant mutants of herpes simplex virus. *J Gen Virol* 1980;49:115-124.
- Byssan YL, Dillion M, Lovett M, et al. Treatment of first episodes of genital herpes simplex virus infection with oral acyclovir: a randomized double-blind controlled trial in normal subjects. *N Engl J Med* 1983;308:916-921.
- Mertz GJ, Critchlow CW, Benedetti J, et al. Double-blind placebo-controlled trial of oral acyclovir in first-episode genital herpes simplex virus infection. *JAMA* 1984;252:1147-1151.
- Nilsen AE, Aasen T, Halsos AM, et al. Efficacy of oral acyclovir in the treatment of initial and recurrent genital herpes. *Lancet* 1982;2:571-573.
- Douglas JM, Critchlow C, Benedetti J, et al. A double-blind study of oral acyclovir for suppression of recurrences of genital herpes simplex virus infection. *N Engl J Med* 1984;310:1551-1556.
- Mindel A, Weller IV, Faherty A, et al. Prophylactic oral acyclovir in recurrent genital herpes. *Lancet* 1984;2:57-59.
- Martin HR, Reichman RC, Benedetti J, et al. Double-blind, placebo-controlled trial comparing long-term suppressive with short-term oral acyclovir therapy for management of recurrent genital herpes. *Am J Med* 1988;85(suppl 2A):20-25.
- Strauss SE, Groen KD, Sawyer MH, et al. Acyclovir suppression of frequently recurring genital herpes. *JAMA* 1988;260:2227-2230.
- Mertz GJ, Elion L, Kaufman R, et al. The Acyclovir Study Group. Prolonged continuous versus intermittent oral acyclovir treatment in normal adults with frequently recurring genital herpes simplex virus infection. *Am J Med* 1988;85(suppl 2A):14-19.
- Goldberg LH, Kaufman R, Conant MA, et al. Episodic twice daily treatment for recurrent genital herpes. *Am J Med* 1988;85:10-13.
- Reichman RC, Badger GJ, Mertz GJ, et al. Treatment of recurrent genital herpes simplex infections with oral acyclovir: a controlled trial. *JAMA* 1984;251:2103-2107.
- Huff JC, Bean B, Balfour HH Jr, et al. Therapy of herpes zoster with oral acyclovir. *Am J Med* 1988;85(suppl 2A):85-89.
- Morton P, Thompson AN. Oral acyclovir in the treatment of herpes zoster in general practice. *NZ Med J* 1989;102:93-95.
- Balfour HH Jr, Kelly JM, Suarez, CS, et al. Acyclovir treatment of varicella in otherwise healthy children. *J Pediatr* 1990;116:633-639.
- Dunkle LM, Arvin AM, Whitley RJ, et al. A controlled trial of acyclovir for chickenpox in normal children. *N Engl J Med* 1991;325:1539-1544.
- Balfour HH Jr, Roitbar HA, Feldman S, et al. Acyclovir treatment of varicella in otherwise healthy adolescents. *J Pediatr* 1992. In press.
- Roitbar HA, Levin MJ, Hayward AR. Immune responses to varicella zoster virus infections in healthy children. *J Infect Dis* 1933;167:195-199.
- Nabb JM, Naiman AJ, Jossey WE, et al. Relation of cytopathology of genital herpesvirus infection to cervical anaplasia. *Cancer Res* 1973;33:1452-1463.
- Douglas JM, David LG, Remington ML, et al. A double-blind, placebo-controlled trial of the effect of chronically administered oral acyclovir on sperm production in man with frequently recurrent genital herpes. *J Infect Dis* 1988;157:588-593.
- Laskin OL, deMiranda P, King DH, et al. Effects of probenecid on the pharmacokinetics and elimination of acyclovir in humans. *Antimicrob Agents Chemother* 1982;21:804-807.
- Stahmann R, Klug S, Lewandowski C, et al. Teratogenicity of acyclovir in rats. *Infection* 1987;15:261-262.
- Lau RJ, Emery MG, Galinsky RE, et al. Unexpected accumulation of acyclovir in breast milk with estimate of infant exposure. *Obstet Gynecol* 1987;69(3):468-471.
- Meyer LJ, deMiranda P, Sheth N, et al. Acyclovir in human breast milk. *Am J Obstet Gynecol* 1988;158(3):586-588.
- Laskin OL, Longstreth JA, Whelton A, et al. Effect of renal failure on the pharmacokinetics of acyclovir. *Am J Med* 1982;73:197-201.
- Krasny HC, Liao SH, deMiranda P, et al. Influence of hemodialysis on acyclovir pharmacokinetics in patients with chronic renal failure. *Am J Med* 1982;73:202-204.
- Bolan J, Schurgers M, Daneels R, et al. Multiple dose pharmacokinetics of intravenous acyclovir in patients on continuous ambulatory peritoneal dialysis. *J Antimicrob Chemother* 1987;20:69-76.
- Shah GM, Winer RL, Krasny HC. Acyclovir pharmacokinetics in a patient on continuous ambulatory peritoneal dialysis. *Am J Kidney Dis* 1986;7:507-510.

MANUFACTURED BY:
ZENITH GOLDLINE PHARMACEUTICALS, INC.
FT. LAUDERDALE, FL 33309

ACYCLOVIR CAPSULES

0172
01/97
01

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074674

CHEMISTRY REVIEW(S)

ADDENDUM

ANDA # 74-674

REVIEW # 3

NAME AND ADDRESS OF APPLICANT

Zenith Goldline Pharmaceuticals, Inc.
140 Legrand Avenue
Northvale, NJ 07647

PROPRIETARY NAME

N/A

NONPROPRIETARY NAME

Acyclovir Capsules 200 mg

AMENDMENT DATE: April 2, 1997

COMMENTS

The applicant indicated that two minor changes were made to the Master Batch Record as follows:

1.

2.

(b)4 - Confidential Business

In support of the changes, the firm submitted release data for their first validation batch of drug product demonstrating conformance to specifications.

CONCLUSIONS AND RECOMMENDATIONS

The changes submitted are minor and should have no significant impact on the drug product. The application may be Approved.

REVIEWER:

Glen Jon Smith

DATE COMPLETED:

April 9, 1997

/S/

4-11-97

/S/

9/4/97

ANDA APPROVAL SUMMARY

ANDA: 74-674

DRUG PRODUCT: Acyclovir USP

FIRM: Zenith

DOSAGE FORM: HG Capsule

STRENGTH: 200 mg

140 LeGrand Avenue
Northvale, NJ 07647

CGMP STATEMENT/EIR UPDATE STATUS:

CGMP statement (p. 251) in original submission, and Section 306(k) certification in New Correspondence, 7/13/95.

EIR acceptable for drug product manufacturer and drug substance manufacturer, 2/23/96. Pre-Approval update requested, 2/14/97.

Facilities included:

Manufacturing, testing, packaging, labeling and stability testing:

Zenith Laboratories, Inc.
140 LeGrand Avenue
Northvale, NJ 07647

Drug Substance Manufacturer:

(b)4 - Confidential Business

Testing:

(b)4 - Confidential Business

BIO STUDY:

Bioequivalence study conducted on the 200 mg capsules Lot #ND-244, batch size (b)4 - capsules was found acceptable by the Division of Bioequivalence per K. Dhariwal, 5/9/96.

In-vitro dissolution study for 200 mg capsules was found acceptable.

VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S):

Drug substance is compendial. Methods for Acyclovir drug product were found to be acceptable by the Philadelphia District Laboratory, 6/4/96. Laboratory description of dosage form was the same as firm's.

STABILITY - ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION?:

Stability for the following included:

<u>Dosage</u>	<u>Lot #</u>	<u>Batch Size</u>	<u>Sample</u>	<u>Test Conditions</u>
200 mg	ND-244	■■■■(b)4 -■■■■	100's	40°C/75% RH/3 months
			500's	25° - 30°C/3 months
			1000's	

Container/Closure system:

(b)4 - Confidential Business

All container/closure systems are as described in the Container/Closure section.

Expiration date: 24 months based on accelerated data.

LABELING:

Description in package insert satisfactory for molecular structure, molecular formula, formula weight, inactive ingredients, product description and package size.

Professional labeling - satisfactory, J. White, 2/18/97.

STERILIZATION VALIDATION (IF APPLICABLE): N/A

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?):

Bio batch: 200 mg product, Lot #ND-244, batch size■■■■(b)4 -■■■■ capsules, stability data included.

■■■■(b)4 - Confidential■■■■ satisfactory, N. Gregory, 2/7/97, no amendments since then.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):

See above.

PROPOSED PRODUCTION BATCH - MANUFACTURING PROCESS THE SAME AS
BIO/STABILITY?:

Executed batch record for the 200 mg x (b)4 - patch Lot #ND-244
(bio/stability batch) included. A blank batch record was
submitted in the application for (b)4 - Confidential
(b)4 - Confidential All scale-ups consistent with
current Office policy. Proposed manufacturing processes are the
same as the bio/stability batches.

CHEMIST:

/S/

DATE:

Mar 6, 1997

SUPERVISOR:

DATE:

3/7/97



Food and Drug Administration
Center for Drug Evaluation and Research
Office of Generic Drugs
Chemistry Division II - Branch VII
Abbreviated New Drug Application Review

1. CHEMISTRY REVIEW NO. 3
2. ANDA # 74-674
3. NAME AND ADDRESS OF APPLICANT
Zenith Laboratories, Inc.
140 LeGrand Avenue
Northvale, New Jersey 07647
4. LEGAL BASIS FOR SUBMISSION
ZOVIRAX® Capsules, 200 mg/capsule
Burroughs Wellcome Co.
3030 Cornwallis Road
Research Triangle Park, NC 27709

Acyclovir is covered by Patent #4199574, Expiration Date April 22, 1997. The firm certified that they will market the product following expiration of the patent. An exclusivity for the treatment of varicella infections expired February 26, 1995.

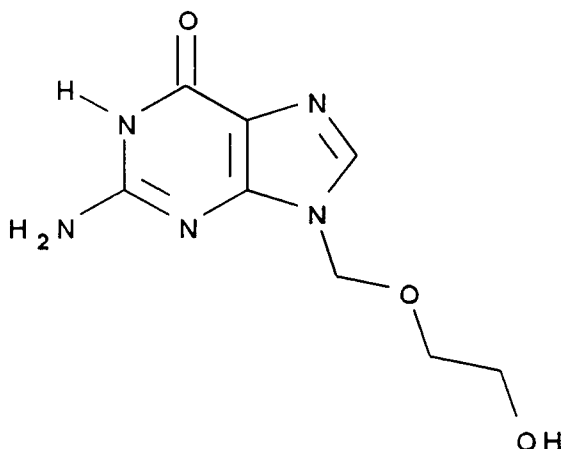
- | | |
|--|--|
| 5. <u>SUPPLEMENT(s)</u>
N/A | 6. <u>PROPRIETARY NAME</u>
N/A |
| 7. <u>NONPROPRIETARY NAME</u>
Acyclovir USP | 8. <u>SUPPLEMENT(s) PROVIDE(s) FOR:</u>
N/A |
9. AMENDMENTS AND OTHER DATES:
- Firm:
- | | |
|---------|--|
| 5/22/95 | Original submission. |
| 7/13/95 | New Correspondence - Response to Agency's request of 7/10/95. |
| 1/12/96 | Amendment - Response to Agency's Incomplete Bioequivalence letter of 11/13/95. |
| 3/11/96 | Notification of Transferral of ANDA |
| 6/13/96 | Amendment - Response to Agency's letter of 12/12/95. |
| 1/29/97 | Amendment - Response to Agency's facimile of 1/16/97. |
- FDA:
- | | |
|----------|--|
| 7/10/95 | Receipt acknowledged. Request for original copy of 306(k) certification. |
| 11/13/95 | Issuance of Incomplete Bioequivalence letter. |
| 12/12/95 | Issuance of Not Approvable letter. |
| 5/3/96 | Issuance of Acknowledgment of Transfer. |
| 5/14/96 | Issuance of Bioequivalence No Further Questions letter. |
| 1/16/97 | Facimile Minor Issued. |
- | | |
|--|----------------------------|
| 10. <u>PHARMACOLOGICAL CATEGORY</u>
Antiviral | 11. <u>Rx or OTC</u>
Rx |
|--|----------------------------|
12. RELATED IND/NDA/DMF(s)

(b)4 - Confidential Business

(b)4 - Confidential Business

13. DOSAGE FORM
HG capsule for oral
administration
14. POTENCIES
200 mg/capsule
15. CHEMICAL NAME AND STRUCTURE

Acyclovir USP
 $C_8H_{11}N_5O_3$; M.W. = 225.21
CAS [59277-89-3]



1. 9-[(2-Hydroxyethoxy)methyl]guanine.
2. 6H-Purin-6-one, 2-amino-1,9-dihydro-9-[(2-hydroxyethoxy)-methyl]-

USP: White to off-white crystalline powder. Melts at temperatures higher than 250°, with decomposition. Soluble in 0.1 N hydrochloric acid; sparingly soluble in water; insoluble in alcohol.

Merck: Crystals from methanol, mp 256.5° - 257°. LD₅₀ in mice (mg/kg): > 10,000 orally; 1000 i.p.

16. RECORDS AND REPORTS
10/30/95 - Chemistry review #1, G.J. Smith.
11/1/95 - Labeling review, L. Golson.
11/4/95 - Bioequivalence review, K. Dhariwal.

5/6/96 - Bioequivalence review, K. Dhariwal.
8/26/96 - Labeling review, J. White.
12/6/96 - Chemistry review #2, G.J. Smith.
2/18/97 - Labeling review, J. White.

17. COMMENTS

The firm has resolved all major questions concerning the chemistry, manufacturing, and controls section of the application.

Labeling was found to be satisfactory, J.White, 2/20/97.

The Division of Bioequivalence found the drug product equivalent, K. Dhariwal, 5/6/96.

Acceptable EIR issued by the Office of Compliance, 2/23/96.
Update requested 2/14/97.

Methods validation found satisfactory, with minor revision recommended, Philadelphia District Laboratory, 6/4/96.

■(b)4 - ■ for drug substance was found satisfactory, N. Gregory,
2/7/97 updated.

18. CONCLUSIONS AND RECOMMENDATIONS

The application may be granted Tentative Approval status.

19. REVIEWER:

Glen Jon Smith

DATE COMPLETED:

March 4, 1997.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER 074674

BIOEQUIVALENCE REVIEW(S)

ANDA 74-674

Zenith Goldline Pharmaceuticals
Attention: Arthur Hurwitz
140 Legrand Ave
Northvale NJ 07647
|||||

MAY 14 1996

Dear Sir:

Reference is made to your abbreviated new drug application submitted pursuant to Section 505 (j) of the Federal Food, Drug and Cosmetic Act for Acyclovir Capsules USP, 200 mg.

1. The Division of Bioequivalence has completed its review and has no further questions at this time.
2. The following dissolution testing will need to be incorporated into your stability and quality control programs:

The dissolution testing should be done in 900 mL of water at 37°C using apparatus 1 (basket) at 100 rpm. The test products should meet the following specifications:

Not less than (b)(4) of the labeled amount of acyclovir in the dosage form is dissolved in 30 minutes.

Please note that the bioequivalency comments expressed in this letter are preliminary. The above bioequivalency comments may be revised after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling or other scientific or regulatory issues. A revised determination may require additional information and/or studies, or may conclude that the proposed formulation is not approvable.

Sincerely yours,

/S/

Keith K. Chan, Ph.D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

OFFICE OF GENERIC DRUGS
DIVISION OF BIOEQUIVALENCE

ANDA # 74-674 SPONSOR: Zenith Laboratories, Inc.
DRUG: Acyclovir
DOSAGE FORM: Capsule
STRENGTHS/(s): 200 mg
TYPE OF STUDY: Single dose; Fasting and Food
STUDY SITE: PharmaKinetics Laboratories, Baltimore, MD 21201

STUDY SUMMARY: Fasting Study: Thirty-two subjects entered the study. Five subjects did not return for phase II. The 90% confidence intervals for $LNAUC_{0-t}$, $LNAUC_{0-inf}$, and LNC_{max} were 85-107%, 87-106%, and 86-109% respectively. AUC_{0-t} and AUC_{0-inf} for the test product were 5% and 4% lower than the respective estimates for the reference product. The C_{max} of test product occurred 12 minutes later and was 3% lower compared to reference product.

Food Study: Eighteen subjects entered the study. Three subjects voluntarily withdrew and one subject was withdrawn because at entry of phase III, his BP readings were 160/102. The test/reference ratios for mean AUC_{0-t} , AUC_{0-inf} , and C_{max} were 0.96, 0.96, and 0.94 respectively. The mean C_{max} for test product was 6% lower than that of the reference product and occurred 7 minutes later.

DISSOLUTION: The dissolution testing was done using FDA method. At 30 min., 10 test capsules dissolved more than (b)4 and 2 capsules dissolved less than (b)4 - Confidential. However, these results pass the acceptance criteria: average of 12 units (92.8%) is equal to or greater than Q (b)4 - Confidential and no unit is less than Q-15%. The results of dissolution tests are acceptable.

PRIMARY REVIEWER: Kuldeep R. Dhariwal, Ph.D, BRANCH: II

INITIAL: (b)4 - Confidential DATE 5/10/96

BRANCH CHIEF: Shriniwas G. Nerurkar, Ph.D., BRANCH: II

INITIAL: (b)4 - Confidential DATE 5/10/96
Business

DIRECTOR
DIVISION OF BIOEQUIVALENCE: Keith Chan, Ph.D

INITIAL: (b)4 - Confidential DATE 5/14/96

DIRECTOR
OFFICE OF GENERIC DRUGS: Roger L. Williams, M.D.

INITIAL: N/A DATE

Not first generic

MAY 9 1996

Acyclovir

200 mg Capsule

ANDA #74-674

Reviewer: Kuldeep R. Dhariwal

File name: 74674SD.196

Zenith Laboratories, Inc.

140 Legrand Avenue

Northvale, NJ 07647

Submission Date:

January 12, 1996

Response to Review of Bioequivalence Study and Dissolution Data

Background:

Zenith Laboratories previously submitted a single-dose *in vivo* bioequivalence study under fasting conditions and dissolution data comparing its acyclovir capsules, 200 mg with Burroughs Wellcome's Zovirax® capsules, 200 mg. Each dose consisted of 400 mg (2 capsules) of either the test or reference product (Filename: 74674SD.595; submission date: May 22, 1995). The bioequivalence study conducted by the firm under fasting conditions and dissolution data were found acceptable. The ANDA was, however, incomplete because the firm had not submitted the food study. The firm submitted the food study as amendment on January 12, 1996 which was received by the Division of Bioequivalence on January 16, 1996. The study (amendment) was assigned to this reviewer on April 8, 1996, who started the review on April 10, 1996.

Bioavailability of Acyclovir Capsules, 200 mg under Fed Conditions:

A. Objective: The objective of this study was (1) to compare the acyclovir plasma levels produced after administration of the test formulation, following a standard meal with those produced after administration of a marketed reference product, after the standard meal and (2) to compare the acyclovir plasma levels produced after administration of the test formulation, following a standard meal with those produced after administration of the test formulation, after an overnight fast.

B. Study Sites and Investigators:

Clinical Site: (b)4 - Confidential Business
Analytical Site: (b)4 - Confidential Business

Medical Director: (b)4 - Confidential Business
Chief Scientific Officer, (b)4 - Confidential Business
Protocol #10848 "Bioavailability of acyclovir capsules, 200 mg:
Effect of food study" was approved by the National Institutional
Review Board for (b)4 - Confidential Business

Consent Form: A copy of volunteer informed consent form used in
the study is given on page 38, vol. 2.1.

Study Dates: Period I January 31 - Feb. 2, 1995
Period II February 7 - Feb. 9, 1995
Period III February 14 - Feb. 16, 1995

Analysis Dates: November 14, 1995 to December 7, 1995

C. Study Design:

A randomized, single-dose, six-sequence, three-way crossover study design was used. The study was executed in three periods with a one week wash-out period between drug administrations. The subjects were housed in a dormitory facility from at least 12 hours before until at least 24 hours after drug administration, each phase. The subjects (who completed the study) were assigned as follows:

Subject #	Period I	Period II	Period III
1,12	A	B	C
2,7,15	C	B	A
3,11,16	A	C	B
4,17	B	C	A
10,13	C	A	B
6,14	B	A	C

A = Acyclovir Capsules, 2 X 200 mg following a standard meal, Zenith Laboratories, Inc.; Lot #ND-244; Lot size: Theoretical Yield: (b)4 - Confidential Business Expiration Date: 8/1995; Manufacture Date: 8/94; Assay: 99.3%; Uniformity of dosage units: 97.6%.

B = Zovirax® Capsules, 2 X 200 mg following a standard meal, Burrough Wellcome Co.; Lot #4N2584; Expiration Date: 3/97; Assay: 99.9%; Uniformity of dosage units: 98.4%.

C = Acyclovir Capsules, 2 X 200 mg following an overnight fast, Zenith Laboratories, Inc.; Lot #ND-244

Formulation: See earlier review (Nov. 4, 1995) for fasting study.

Lot numbers of drug products administered in this study were the same as those used for the fasting study.

D. Subject Selection:

Eighteen healthy male subjects were enrolled in the study. Following inclusion criteria were used in selecting the subjects:

- male, healthy, 18-50 years of age
- no more than $\pm 15\%$ from ideal weight for their height as defined by Metropolitan Life Insurance Company Statistical Bulletin 1983
- good health as determined by medical histories and physical examinations. Blood chemistry, hematology, and urinalysis values within clinically acceptable limits, obtained within 30 days prior to the start of the study

Subjects were excluded from this study based on the following criteria:

- history of asthma, chronic bronchitis, herpes, hypertension, cardiovascular, neurological, hepatic, renal, hematopoietic, gastrointestinal or ongoing infectious diseases
- history of alcohol or drug abuse
- positive HIV-1, hepatitis B surface antigen
- blood pressure lower than 100/60 mm Hg at screening or check-in
- known allergy to acyclovir or to related drugs

Subjects were imposed with following restrictions:

- no prescription drugs within 14 days (excluding contraceptives) or OTC medications (excluding OTC ibuprofen, aspirin, acetaminophen, vitamins, medicated lozenges, dietary supplements, and non-ingested medications) within 7 days of the first drug administration
- no alcohol consumption for at least 24 hours prior to drug administration
- no caffeine for at least 12 hours prior to dosing
- no smoking from 1 hour prior to dosing until 4 hours following drug administration

E. Sample Collection:

Ten milliliters of venous blood were obtained in heparinized Vacutainers® at 0 (predose), 0.33, 0.67, 1, 1.33, 1.67, 2, 2.5, 3, 3.5, 4, 5, 6, 8, 10, 12, 14, 16 and 24 hours postdose. Samples were centrifuged within 15 minutes of acquisition. The plasma was transferred to prelabeled polypropylene tubes and promptly frozen at -20°C .

F. Analytical Methods:

(b)4 - Confidential Business

(b)4 - Confidential Business

G. Pharmacokinetics/Statistical Analysis:

The area under the plasma concentration versus time curve was calculated using the linear trapezoidal rule from the zero time point to the last quantifiable concentration. The area under the plasma concentration versus time curve from zero to infinity was calculated by adding C_t/K_{elm} to AUC_{0-t} where C_t is the last quantifiable concentration and K_{elm} is the elimination rate constant. The maximum observed plasma concentration (C_{max}) and time to maximum plasma concentration (T_{max}) were obtained by inspection. The terminal elimination rate constant was obtained from the slope of the line, fitted by linear least squares regression, through the terminal points of the log(base e) of the concentration versus time plot for these points. The half-life was calculated by the equation $T_{1/2} = 0.693/K_{elm}$. The statistical analyses were performed using SAS software. The calculations for the 90% confidence interval about the ratio of the mean test value to mean reference value and for the power of the ANOVA to detect a 20% difference from the reference mean were performed using the LSMEAN values and standard error of estimate values as generated by SAS. The ratios of geometric means and the 90% confidence intervals of the log (base e) transformed data were calculated for AUC_{0-t} , AUC_{0-inf} , and C_{max} .

H. Results:

1. Clinical:

Eighteen subjects entered the study. Subject #18 failed to return after completing period I, subject #5 and 9 did not return for

period III. Subject #8 was withdrawn from the study by the physician because of increased blood pressure measurements. The plasma samples from fourteen subjects who completed the study were assayed for acyclovir. Clinical vital signs were measured at 0, 4 and 24 hours. Diagnostic blood and urine specimens were obtained from the subjects prior to discharge from the study at the end of period III. Following subjects showed poststudy laboratory results outside of the reference range and require follow-up tests and evaluation:

Subject #	Test result
1	Blood, RBC/HPF in urine
17	Blood, RBC/HPF in urine

Adverse events:

Following six subjects experienced adverse events during the study. All events were mild in severity.

Subject #	Period	Product	Sign/Symptom
6	III	Test(fasted)	1 centimeter raised pruritic bump left lateral elbow
8	III	Test(fasted)	sore throat; increased blood pressure
10	II	Test(fed)	headache, increased diastolic blood pressure
11	II	Test(fed)	headache
16	III	Ref(fed)	cold symptoms
17	II	Test(fasted)	lightheaded, headache*
		Test(fed)	1 pruritic hive right deltoid

* Self-administered 1 tablet of Advil 200 mg

Deviations in the study:

There was one deviation in scheduled phlebotomy time. A deviation was defined as greater than 5% of the time since dosing for samples up to 10 hours, and greater than 30 minutes for samples thereafter. For subject #6 in period I (reference-fed) the 20 minute sample was delayed by 4 minutes. Actual time was used for AUC calculations.

Subject 1, period 2, 24 hour samples was not received by the analytical lab from the clinic.

Reassays:

Of the 797 samples assayed, 20 samples were reassayed. Following samples were reassayed for the reasons shown against them:

# of samples	Reason for reassay
5	Integrator malfunction
12	Chromatographic interference
2	Anomalous value
1	Value for predose sample

2. Analytical:

(b)4 - Confidential Business